Seventy-First Meeting of the

Obstetrics and Gynecology Devices Panel

Monday, March 27, 2006
Gaithersburg Hilton, Gaithersburg, MD

Innovata plc, Adept® Adhesion Reduction Solution (P050011)

Panel Discussion Questions

1. There were three co-primary endpoints in the pivotal clinical trial of Adept®. Success of the clinical trial was defined such that all three co-primary endpoints were to be met. Two of these endpoints compared Adept® to Lactated Ringer's Solution (LRS). The first of these looked at the percent of patients in each arm of the study who met the definition of a "success" and the third was the percent of patients with fewer sites with dense adhesions at second look. For those two endpoints, the study objectives were not met. The other co-primary endpoint (2nd) compared the number of adhesions in the Adept® group at first and second look to determine whether adhesion burden got worse in the Adept® patients. For this endpoint, Adept® demonstrated a statistically significant reduction in adhesions.

   Intent-to-Treat (ITT) results are presented in the table below:

Pivotal Study: Primary Effectiveness Endpoints (ITT), Ref. Table 12

	Adept®	**Control**
Total number of patients	227	222
Patient Success		
Number reporting	103 (45.4%)	79 (35.6%)
Difference in % of patients with success	9.8%	
95.2 CI for % of patients with success	(**0.7%**, 18.9%)	
Number of sites with adhesions		
1st look (mean±sd)	10.27±4.26	10.34±4.39
2nd look (mean±sd)	7.88±4.64	8.49±4.98
Change from 1st to 2nd look (mean±sd)	-2.40±3.66	-1.86±3.35
LS mean for change* (95.2% CI)	**-2.22 (-2.83, -1.62)**	-1.60 (-2.24, -0.96)
p-value for change	**<0.001**	<0.001
Difference between LS means	-0.62	
95.2% CI	(-1.24, -0.004)	
p-value for treatment	0.047	
Percentage of patients with fewer sites with dense adhesions		
# of patients with fewer dense adhesion sites at second look (%)	114 (50.2%)	109 (49.1%)
p-value for difference between 2 arms	**0.73**	
1st look (mean±sd)	6.17±4.74	6.23±5.26
2nd look (mean±sd) (n)	5.02±4.60 (212)	5.25±5.26 (208)
change from 1st to 2nd look (mean±sd) (n)	-1.19±3.43 (212)	-1.01±3.24 (208)
p-value for change	<0.001	<0.001

* least-square mean for change, adjusted for center and baseline

   Although the statistical hypothesis for only one of the co-primary endpoints was met, please discuss **each** of the primary endpoints considering the objective, the statistical test and the clinical significance.

2. Ten secondary endpoints were pre-specified in the pivotal study, several with multiple components. Per protocol (PP) results are presented in the table below:

Pivotal Study: Secondary Effectiveness Endpoints (PP), Ref. Table 13

Endpoint / Variable	Adept®	Control	P-value*
Incidence of sites with adhesions			
Change from 1st to 2nd look	-2.64 ± 3.66	-2.02 ± 3.19	0.039
% patients with reduction	76.4%	69.3%	0.121
Change from 1st to 2nd look excluding non-lyzed sites	-2.64 ± 3.66	-2.02 ± 3.19	0.068
% patients with four or fewer sites with adhesions at 2nd look	32.0	28.1	0.510
Shift analysis - % patients with 2nd look incidence grouped Into 4 categories	0: 4.9 1-4 27.1 5-9 36.0 ≥10 32.0	0: 4.5 1-4 23.6 5-9 31.7 ≥10 40.2	0.173
Severity of sites with adhesions			
% change from 1st to 2nd look per patient	-24.2 ± 45.2	-21.5 ± 41.0	0.415
% patients with reduction	72.9%	69.8%	0.446
Extent of sites with adhesions			
% change from 1st to 2nd look per patient	-26.9 ± 51.4	-21.8 ± 48.5	0.240
% patients with reduction	77.3%	69.8%	0.084
AFS score			
Change from 1st to 2nd look for patients with a primary diagnosis of infertility	(n=102) -3.46 ± 6.77	(n=112) -1.10 ± 6.36	0.011
% patients with reduction for patients with a primary diagnosis of infertility	**52.9%**	**30.4%**	**0.001**
Shift analysis - % patients with 2nd look scores grouped Into 4 categories	(n=102) minimal: 68.6 mild: 10.8 moderate: 11.8 severe: 8.8	(n=112) minimal: 59.8 mild: 13.4 moderate: 15.2 severe: 11.6	0.066
Modified AFS score			
Change from 1st to 2nd look	-0.67 ± 1.54	-0.48 ± 1.61	0.094
% patients with reduction	70.4%	69.8%	0.722
Reformed adhesions			
Number of sites with reformed adhesions	4.92 ± 3.91	5.11 ± 4.12	0.722
Number of sites without reformed adhesions	3.77 ± 2.72	3.32 ± 2.29	0.065
% patients with at least one	87.7%	86.9%	0.832
***De novo* adhesions**			
Number of sites with	1.13 ± 1.85	1.29 ± 1.61	0.036
% patients with at least one	47.3%	57.3%	0.029
Abdominal wall adhesions			
Change from 1st to 2nd look in number of sites	-1.17 ± 1.63	-0.94 ± 1.60	0.184
% patients with reduction from 1st to 2nd look in no. sites	65.5%	58.3%	0.129
Visceral adhesions			
Change from 1st to 2nd look in number of sites	-1.47 ± 2.62	-1.07 ± 2.22	0.046
% patients with reduction from 1st to 2nd look in no. sites	68.5%	63.3%	0.228
VAS score for pelvic pain			
Change from screening to 2nd look for patients with primary diagnosis of pelvic pain	(n=118) -35.8 ± 32.8	(n=108) -30.8 ± 30.2	0.995

*** not adjusted for multiplicity**

From a statistical perspective, secondary endpoints are of limited value in demonstrating study success. On inspection (table above), the observed results for most of these endpoints favor Adept®; however, after multiplicity adjustments, only one endpoint – the percent of infertility patients with a reduction in AFS score – still appears to be statistically significant.

Please discuss the statistical and the clinical significance of the above secondary outcomes. In particular, please focus on the data for subjects with a primary diagnosis of infertility.

3. In the pivotal trial, there were four serious adverse events possibly related to treatment (two Adept® and two LRS patients).

Serious Adverse Events possibly related to the treatment (Ref: Table 17)

Center #/Patient #/treatment	Days post op	Age	SAE	Duration and severity	Details
13/637[a] **Adept®** Vol. 2 Page 372-4	Same day	42	Inability to void, labial swelling, ecchymoses at port site, nausea, vomiting	All lasted 1-2 days except ecchymoses which lasted 12 days. Urinary was severe, all else moderate	Admitted day of surgery for inability to void, observed overnight with intermittent catheterization and developed ecchymoses, nausea and vomiting. Discharged on second day of hospitalization
14/485 **Adept®** Vol. 4 Pages 375-8	Same day	25	Pain in pelvis, chest, shoulder, abdomen, nausea, dysuria, urinary frequency	1-7 days, All severe	Pt with h/o chronic pelvic pain. Admitted two days after surgery, only finding noted was pneumoperitoneum, nausea from sound of fluid moving around in her stomach, urinary frequency developed in hospital
14/555 **LRS** Vol. 4 Pages 420-2	4	23	Severe abdominal pain, nausea, vomiting, lower back pain	1-2 days, all severe except back pain which was moderate	Initial ER visit was Day of surgery, followed up with office visit with acute abdominal pain followed by nausea and vomiting and hosp for observation, (-) CT scan. Symptoms resolved spontaneously,
13/073 **LRS** Vol. 4 Page 183	2	43	Decreased urinary output, elevated creatinine	Both events 2 days	Admitted for 2-days, catheterized, given IV fluids, discharged

[a] This event was considered by the investigator as unrelated to Adept®.

In addition, vulvar edema, a side effect of Adept® use, occurred in approximately 6% of the subjects in the pivotal trial. In the European market experience, vulvar edema was reported at a 0.03-0.04% incidence.

Please discuss the safety data from the pivotal trial and identify any adverse events, including vulvar edema, you believe may be related to Adept®. Also, please discuss whether you believe that the risk posed by Adept® is outweighed by the clinical benefit as discussed under Questions 1 and 2 above.

4. Innovata established a registry (ARIEL) for Adept®, and captured data on 4620 surgical patients (2882 gynecological and 1738 general surgery). Data was collected between February 2000 and December 2003 from "leading centers" in five European countries. It is estimated that Adept® was used on 65,000 patients while the registry was in effect.

Top five adverse events in 2,069 ARIEL gynecological laparoscopy patients (Ref: Table 18.)

Adverse Event	ARIEL
	Number (%)
Pyrexia	10 (0.5)
Device failure	9 (0.4)
Abdominal pain	5 (0.2)
Abdominal distension	5 (0.2)
Urinary retention	5 (0.2)

Please discuss whether the safety data from the ARIEL registry supports the safe use of Adept® as an adhesion prevention solution.

Labeling & Training

5. Does the panel have any comments on the labeling provided by the sponsor?

Post-approval Study

6. CDRH sometimes requires post-approval studies to help monitor safety, effectiveness and reliability of marketed medical devices. These studies are conducted under a FDA-approved protocol with the intended purpose of gathering specific additional information about marketed devices. Some of the reasons for conducting post-approval studies include the evaluation of longer-term device performance, performance in broader patient and user populations, performance in specific sub-groups of patients, or evaluation of certain rare outcomes of interest. Although post-approval studies should answer important post-market questions, they should not be used to evaluate unresolved issues from the premarket phase that are essential to the initial assurance of reasonable device safety and effectiveness.

   Does the panel have input regarding any issues that should be addressed in a post-approval study?